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(54) Title: COMPOSITIONS COMPRISING A CYCLOOXYGENASE-2 INHIBITOR AND A 5-LIPOXYGENASE INHIBITOR

(57) Abstract

Combinations of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor are described for treatment of inflammation and inflammation-related disorders.

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# COMPOSITIONS COMPRISING A CYCLOOXYGENASE-2-INHIBITOR AND A 5-LIPOXYGENASE INHIBITOR

5

## FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to co-  
10 administration of an inhibitor of cyclooxygenase-2 and a 5-lipoxygenase inhibitor for treating inflammation and inflammation-related disorders, such as arthritis.

## BACKGROUND OF THE INVENTION

15

Prostaglandins play a major role in the inflammation process, and the inhibition of prostaglandin production, especially production of PGG<sub>2</sub>, PGH<sub>2</sub> and PGE<sub>2</sub>, has been a common target of  
20 antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process.  
25 Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids,  
30 which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or

"prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

5        In another portion of the arachidonic acid pathway, physiologically active leukotrienes, such as leukotriene B<sub>4</sub> (LTB<sub>4</sub>), leukotriene C<sub>4</sub> (LTC<sub>4</sub>) and leukotriene D<sub>4</sub> (LTD<sub>4</sub>) and other metabolites, are produced by the 5-lipoxygenase-mediated (5-LO) 10 oxidation of arachidonic acid. These leukotrienes have been implicated in various inflammation-related disorders and allergic diseases, and thus compounds which inhibit leukotriene A<sub>4</sub> conversion to leukotriene B<sub>4</sub>, such as compounds which inhibit leukotriene A<sub>4</sub> 15 hydrolase are useful in the treatment of disease states in which leukotrienes play an important role.

It is believed that selective inhibitors of cyclooxygenase-2 and of leukotriene A<sub>4</sub> hydrolase, which affect the two enzymes at low concentrations, will 20 decrease the incidence and severity more completely. These compositions also will beneficially affect the damage caused by the various inflammatory diseases and inflammation-related disorders mediated by cyclooxygenase-2 and leukotriene A<sub>4</sub> hydrolase. These 25 compositions also will not have the level of gastrointestinal side effects commonly associated with traditional NSAIDs.

Compounds which selectively inhibit cyclooxygenase-2 have been described in U.S. patents 30 5,380,738, 5,344,991, 5,393,790, 5,466,823, 5,434,178, 5,474,995, 5, 510,368 and WO documents WO96/06840, WO96/03388, WO96/03387, WO95/15316, WO94/15932, WO94/27980, WO95/00501, WO94/13635, WO94/20480, and WO94/26731.

35        Compounds which inhibit 5-lipoxygenase have been described. U.S. Patent No. 5,234,950 describes tetrahydrofuran derivatives. U.S. Patent No. 5,098,932

describes cyclic ether derivatives. U.S. Patent No. 5,354,865 describes tetrahydropyrans. Acetylene derivatives have been described as having 5-LO activity in WO92/01682.

5 Compounds which inhibit cyclooxygenase and 5-lipoxygenase have been described. U.S. Patent No. 5,298,521 describes pyrazole thiocarbamates. U.S. Patent No. 5,242,940 describes pyrazoles as inhibiting both enzymes. U.S. Patent No. 5,356,898 describes di-  
10 tertbutylpyrimidines. However, these previous mixed inhibitors do not selectively inhibit cyclooxygenase-2 and therefore still cause the gastrointestinal side effects which substantially reduce their usage and effectiveness.

15 Combined therapies of NSAIDs and other reagents are known in the art. Brooks and Karl describe the treatment of hay fever with combined antihistamines and a cyclooxygenase-inhibiting drug (flurbiprofen) (J. Allergy Clin. Immunol., **81**, 110 (1988)). J. Basmajian  
20 (Spine, **14**, 438 (1989)) describes the combination of the analgesic diflunisal and an antispasm agent in the treatment of back pain. V. Fossaluzza and S. DeVita describe the combined therapy of ibuprofen and an antispasm agent to reduce morning stiffness associated  
25 with primary fibromyalgia syndrome (Int. J. Clin. Pharm. Res., **XII**, 99 (1992)). R. Greenwald et al. (J. Rheumatol., **19**, 927 (1992)) report the combination of tetracycline and the NSAID flurbiprofen ameliorates the tissue damage associated with rheumatoid arthritis.

30 Combination analgesics have been reported (W. Beaver, Am. J. Med., **77**, 38 (1984)) although such combinations do not substantially reduce adverse effects.

35 The combination of NSAIDs and steroids have been described. A combination of indomethacin, steroid and lipopolysaccharide has been reported for the treatment of spinal injury (L. Guth et al., Proc. Natl. Acad.

Sci. USA, **91**, 12308 (1994)). G. Hughes *et al.* describe combinations of corticosteroids with NSAIDs for the treatment of sunburn (Dermatology, **184**, 54 (1992)). C. Stewart *et al.* (Clin. Pharmacol. Ther., **47**, 540 (1990)) describe the combination of naproxen and methotrexate as safe, although concurrent 5 administrations of methotrexate with other NSAIDs have been reported to be toxic and sometimes fatal. A combination of a dual 5-lipoxygenase/cyclooxygenase 10 inhibitor with a glucocorticoid is described for the treatment of skin disorders (K. Trampisch, Inflammation, **17**, 531 (1993)). Combinations of NSAIDs and steroids should be used in the treatment of scleritis only if patients are not responsive to any 15 other treatment (S. Lightman and P. Watson, Am. J. Ophthalmol., **108**, 95 (1989)).

Combinations of cyclooxygenase inhibitors, lipoxygenase inhibitors, collagenase inhibitors and cytotoxic agents have been used in the treatment of 20 non-small-cell lung cancers (B. Teicher *et al.*, Cancer. Chemother. Pharmacol., **33**, 515 (1994)).

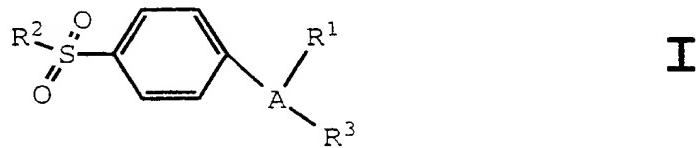
Combinations of naproxen with other NSAIDs have been described in the treatment of arthritis. R. Willikens and E. Segre (Arthritis Rheum., **19**, 677 (1976)) describe the combination of aspirin and naproxen as being more effective than aspirin alone for the treatment of rheumatoid arthritis. Naproxen and acetaminophen together were described for treating the pain associated with arthritis (P. Seideman *et al.*, Acta Orthop. Scand., **64**, 285 (1993)). However, 25 combinations of naproxen with indomethacin or ibuprofen offer no advantage in the treatment of arthritis (M. Seifert and C. Engler, Curr. Med. Res. Opin., **7**, 38 (1980)). European patent document EP485,111, published 30 May 13, 1992, describes the synergistic combination of lipoxygenase inhibitors and NSAID's for the treatment of inflammatory disease.

There have been no reported combinations of a cyclooxygenase-2 selective inhibitor and a 5-lipoxygenase inhibitor.

5                   **DESCRIPTION OF THE INVENTION**

The invention involves a method of treating a subject having inflammation or an inflammation-related disorder with a combination comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor.

In addition, the invention describes a combination comprising a therapeutically-effective amount of a 5-lipoxygenase inhibitor and a cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



20                 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

25                 wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

30                 wherein R<sup>2</sup> is methyl or amino; and

35                 wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl,

heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl,  
acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl,  
aryl carbonyl, aralkyl carbonyl, aralkenyl, alkoxy alkyl,  
arylthio alkyl, aryloxy alkyl, aralkylthio alkyl,  
5 aralkoxy alkyl, alkoxy aralkoxy alkyl, alkoxy carbonyl alkyl,  
aminocarbonyl, aminocarbonyl alkyl, alkylaminocarbonyl,  
N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl,  
alkylaminocarbonyl alkyl, carboxy alkyl, alkyl amino, N-  
arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-  
10 alkyl-N-arylamino, amino alkyl, alkylamino alkyl, N-  
arylamino alkyl, N-aralkylamino alkyl, N-alkyl-N-  
aralkylamino alkyl, N-alkyl-N-arylamino alkyl, aryloxy,  
aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-  
15 arylaminosulfonyl, arylsulfonyl, N-alkyl-N-  
arylamino sulfonyl; or a pharmaceutically-acceptable  
salt thereof.

Combinations of the invention would be useful for,  
but not limited to, the treatment of inflammation in a  
20 subject, and for treatment of other inflammation-  
associated disorders, such as, as an analgesic in the  
treatment of pain and headaches, or as an antipyretic  
for the treatment of fever. For example, combinations of  
the invention would be useful to treat arthritis,  
25 including but not limited to rheumatoid arthritis,  
spondyloarthropathies, gouty arthritis, osteoarthritis,  
systemic lupus erythematosus and juvenile arthritis.  
Such combinations of the invention would be useful in  
30 the treatment of asthma, bronchitis, menstrual cramps,  
tendinitis, bursitis, and skin related conditions such  
as psoriasis, eczema, burns and dermatitis. Combinations  
of the invention also would be useful to treat  
gastrointestinal conditions such as inflammatory bowel  
35 disease, Crohn's disease, gastritis, irritable bowel  
syndrome and ulcerative colitis and for the prevention  
or treatment of cancer, such as colorectal cancer.  
Combinations of the invention would be useful in

treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis.

The compounds would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The combinations of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. As inhibitors of 5-lipoxygenase, these compositions would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma. Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc..

The term "cyclooxygenase-2 inhibitor" embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC<sub>50</sub> of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC<sub>50</sub>

of greater than about 1  $\mu\text{M}$ , and more preferably of greater than 20  $\mu\text{M}$ . Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

5       The term "5-lipoxygenase inhibitor" embraces compounds which selectively inhibit 5-lipoxygenase with an IC<sub>50</sub> of less than about 10  $\mu\text{M}$ . More preferably, the 5-lipoxygenase inhibitors have a 5-lipoxygenase IC<sub>50</sub> of less than about 1  $\mu\text{M}$ .

10      The phrases "combination therapy", "co-administration" or "co-therapy", in defining use of a cyclooxygenase-2 inhibitor agent and a 5-lipoxygenase inhibitor agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial 15 effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

20      The phrase "therapeutically-effective" is intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in inflammation severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse 25 side effects typically associated with alternative therapies.

Preferred 5-lipoxygenase inhibitors include masoprolol, tenidap, zileuton, Abbott A-76745, N'-[(5-(4-fluorophenoxy)furan-2-yl)-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-78773), (R)(+)-[(5-(4-fluorophenoxy)furan-2-yl)-30 1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175), Abbott ABT 761, Dainippon AL-3264, Bayer Bay-x-1005, Biofor BF-389, bunaprolast, Ciba-Geigy CGS-25997, Cytomed CMI-392, Cytomed CMI-568, Atlantic Pharmaceutical CT3, Takeda CV-6504, Efamol EF-40, enazadrem phosphate, Leo Denmark ETH-615, flezelastine 35 hydrochloride, flobufen, Merck Frosst L 663536, Merckle ML-3000, linazolast, lonapalene, Mercian MER W8020, N-hydroxy-N-[1-(2-phenyl-5-benzofuranyl)ethyl]urea (R. W. Johnson

Research Institute), ontazolast, 3M Pharmaceuticals R-840, rilopirox, Hoechst Marion Roussel RU54808, Schering Plough SCH 40120, tepoxalin, Tanabe 757, Tanabe 799, Terumo TMK-688, Glaxo Wellcome WILD20, Zeneca ZD-2138, Abbott A-121798,  
5 Abbott A 72694, Abbott A-80263, Biofor BF-397, Bristol-Myers Squibb BU-4601A, carbazoycin C, lagunamycin, Wellcome BW-70C, Ciba-Geigy CGS-26529, Warner-Lambert CI 1004, Warner-Lambert PD-136005, Warner-Lambert PD-145246, Eisai E 3040, Fujirebio F-1322, Fisons FPL-64170, Fujisawa FR 110302, Nippon Hypox HX  
10 0386, Merck & Co L-699333, Merck Frosst L 739010, Lilly LY-269415, Lilly LY 178002, Meiji Milk MM-7002, Hoechst Roussel P 8892, Hoechst Roussel P 8977, Hoechst Roussel HP977, SmithKline Beecham SB-202235, Green Cross SS-81-OH, Terumo Keio University TMK 685, American Home Products WAY-121520,  
15 American Home Products WAY-125007, Zeneca ZD 7717, Zeneca ZM-216800, Zeneca ZM 230487, 1,2-dihydro-n-(2-thiazolyl)-1-oxopyrrolo(3,2,1-k1)phenothiazine-1-carboxamide, Abbott A-65260, Abbott A-69412, Abbott Abbott-63162, American Home Products AHR-5333, Bayer Bay-q-1531, Boehringer Ingelheim BI-L-357, Boehringer Ingelheim BI-L-93BS, Boehringer Ingelheim BIL 226XX, Bristol-Myers Squibb BMY-30094, carbazomycin B, Wellcome BW 4C, Wellcome BW-B218C, Wellcome BW-B70C, Chauvin CBS-1114, Ciba-Geigy CGS-21595, Ciba-Geigy CGS-22745, Ciba-Geigy CGS-23885, Ciba-Geigy CGS 24891, Ciba-Geigy CGS-8515,  
20 25 Chiesi CHF-1909, Warner-Lambert CI-986, Warner-Lambert CI 987, cirsiliol, docebenone, DuPont Merck DuP-654, Eisai E 5110, Eisai E-6080, Green Cross EN-105, enofelast, epocarbazolin-A, eprovafen, evandamine, forsythiaside, Fisons FPL 62064, Glaxo GR-80907, Zeneca ICI-211965, isoflavans,  
Kyowa Hakko KF-8940, Merck & Co L-651392, Merck & Co L-  
30 651896, Merck & Co L-652343, Merck & Co L-656224, Merck & Co L-670630, Merck & Co L-674636, Merck & Co L-691816, Lilly LY-233569, Lilly LY-280810, Merck & Co MK-591, Merck & Co MK-886, nitrosoxacin-A, Ono ONO-5349, Ono ONO-LP-219, Ono ONO-  
35 LP-269, Warner-Lambert PD-127443, Purdue Frederick PF-5901, Sandoz QA-208-199, Johnson & Johnson R-68151, Johnson & Johnson R-85355, Rhone-Poulenc Rorer Rev-5367, Rhone-Poulenc

Rorer RG-5901-A, Rhone-Poulenc Rorer RG-6866, Roussel-Uclaf RU-46057, Searle SC-41661A, Searle SC-45662, Sandoz SDZ-210-610, SmithKline Beecham SK&F-104351, SmithKline Beecham SK&F-104493, SmithKline Beecham SK&F-105809, Synthelabo SL-81-  
5 Teijin TEI-8005, Terumo TMK-777, Terumo TMK-781, Terumo TMK-789, Terumo TMK-919, Terumo TMK-992, Teikoku Hormone TZI-2721, Teikoku Hormone TZI-41127, American Home Products WAY-120739, American Home Products WY 47288, American Home Products Wy-48252, American Home Products Wy-50295, and  
10 Yoshitomi Y-19432.

More preferred 5-lipoxygenase inhibitors include ibudilast, masoprolol, tenidap, zileuton, Abbott A-121798, Abbott A-76745, N'-[ [5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-  
15 78773), (R) (+)N'-[ [5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175), Abbott ABT 761, Dainippon AL-3264, Bayer Bay-x-1005, Biofor BF-389, bunaprolast, Cytomed CMI-392, Cytomed CMI-568, Atlantic Pharmaceutical CT3, Takeda CV-6504,  
20 Ciba-Geigy CGS-26529, Ciba-Geigy CGS-25997, enazadrem phosphate, Eisai E 3040, Leo Denmark ETH-615, flezelastine hydrochloride, flobufen, Fujirebio F-1322, Hoechst Roussel HP977, linazolast, lonapalene, Merck Frosst L 663536, Merck Frosst L 699333, Merckle ML-3000,  
25 Mercian MER W8020, N-hydroxy-N-[1-(2-phenyl-5-benzofuranyl)ethyl]urea (R. W. Johnson Research Institute), ontazolast, Hoechst Roussel P 8892, Hoechst Roussel P 8977, Warner-Lambert PD-145246, Purdue Frederick PF-5901, 3M Pharmaceuticals R-840, rilopirox,  
30 Hoechst Marion Roussel RU54808, Schering Plough SCH 40120, Tanabe 757, Tanabe 799, tepoxalin, Terumo TMK-688, Scotia Pharmaceuticals EF-40, Glaxo Wellcome WILD20, Zeneca ZD 7717, and Zeneca ZD-2138.

Even more preferred 5-lipoxygenase inhibitors  
35 include ibudilast, masoprolol, tenidap, zileuton, Abbott A-76745, N'-[ [5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-78773), (R) (+)N'-[ [5-

(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175), Abbott ABT 761, Bayer Bay-x-1005, Cytomed CMI-392, Ciba-Geigy CGS-26529, Biofor BF-389, Cytomed CMI-392, Eisai E 3040, Scotia

5 Pharmaceuticals EF-40, Leo Denmark ETH-615, flobufen, Fujirebio F-1322, linazolast, ionapalene, Merck Frosst L 699333, Merckle ML-3000, ontazolast, Purdue Frederick PF-5901, 3M Pharmaceuticals R-840, rilopirox, Terumo TMK-688, and Zeneca ZD-2138.

10 A preferred class of compounds which inhibit cyclooxygenase-2 consists of compounds of Formula I wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed 15 heterocyclyl, lower cycloalkenyl and phenyl; wherein R<sup>1</sup> is selected from 5- and 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more 20 radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R<sup>2</sup> is 25 methyl or amino; and wherein R<sup>3</sup> is a radical selected from hydrido, oxo, cyano, carboxyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl, 30 lower hydroxylalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenoxy, and lower aralkoxy; or a 35 pharmaceutically-acceptable salt thereof.

A more preferred class of compounds which inhibit cyclooxygenase-2 consists of compounds of Formula I

wherein A is selected from oxazolyl, isoxazolyl, furyl, thienyl, dihydrofuryl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R<sup>1</sup> is

5 selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, fluoromethyl, cyano, difluoromethyl, trifluoromethyl, carboxyl, hydroxyl, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl, trifluoromethoxy, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and methylthio; wherein R<sup>2</sup> is methyl or amino; and wherein R<sup>3</sup> is a radical selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxymethyl, hydroxylpropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethoxy, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, benzyloxy, and phenoxy; or a pharmaceutically-acceptable salt thereof.

35 A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;  
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-  
5 3-(trifluoromethyl)pyrazole;  
4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide  
4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
10 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-  
15 yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-  
20 yl)benzenesulfonamide;  
4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide  
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
25 yl]benzenesulfonamide;  
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-  
30 yl]benzenesulfonamide;  
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
35 yl]benzenesulfonamide;  
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
40 yl]benzenesulfonamide;  
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-  
45 yl]benzenesulfonamide;  
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
50 yl]benzenesulfonamide;  
4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-  
55 pyrazol-1-yl]benzenesulfonamide;  
4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-  
60 yl]benzenesulfonamide;

- 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 20 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 25 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 30 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 35 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;  
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;  
5 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;  
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;  
2-[ (3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;  
10 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;  
1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;  
15 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;  
5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;  
4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-  
20 yl]benzenesulfonamide;  
6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;  
2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;  
25 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;  
4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-  
30 imidazol-1-yl]benzenesulfonamide;  
4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
35 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;  
5 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;  
10 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;  
2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;  
15 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;  
2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;  
1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;  
20 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;  
4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
25 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;  
4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;  
2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;  
30 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;  
1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;  
35 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;  
4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;  
5 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;  
4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;  
N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-  
10 5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;  
ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;  
4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;  
15 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;  
1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;  
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-  
20 trifluoromethyl-1H-imidazole;  
4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;  
5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-  
25 6-(trifluoromethyl)pyridine;  
2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-  
6-(trifluoromethyl)pyridine;  
5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynloxy)-6-(trifluoromethyl)pyridine;  
2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;  
30 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-  
35 phenylisoxazole;  
4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

- 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
5 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;  
1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
10 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
15 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
20 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;  
1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-  
25 yl]benzenesulfonamide;  
4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;  
1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
30 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-  
35 yl]benzenesulfonamide;  
1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;  
4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-  
y1]benzenesulfonamide;

4-[2-(2-methylpyridin-5-yl)cyclopenten-1-  
y1]benzenesulfonamide;  
ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)  
phenyl]oxazol-2-yl]-2-benzyl-acetate;  
5 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;  
2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;  
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-  
10 phenyloxazole;  
4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and  
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-  
oxazolyl]benzenesulfonamide.

15

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH<sub>2</sub>-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl,

allyl, propenyl, butenyl and 4-methylbutenyl. The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl  
5 radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like. The terms "alkenyl", "lower alkenyl",  
10 embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals  
15 having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred  
20 cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl. The term "halo" means halogens such as fluorine, chlorine, bromine or  
25 iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for  
30 one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals.  
35 "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl,

trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents

selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, 5 aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

The term "heterocyclyl" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of

10 saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2

15 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals

20 include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of unsaturated heterocyclyl radicals, also termed

25 "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl

30 (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g.,

35 tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thietyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, 10 benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; 15 unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclyl radicals are fused with aryl radicals. Examples of 20 such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino. The term "alkylthio" embraces radicals containing a linear 25 or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are 30 methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl 35 radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include

methylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent  $-S(=O)-$  radical. More preferred alkylsulfinyl radicals  
5 are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other  
10 terms such as alkylsulfonyl, denotes respectively divalent radicals  $-SO_2-$ . "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl"  
15 radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or  
20 bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote  $NH_2O_2S-$ . The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include  
25 alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl. The term "carbonyl", whether used alone or with other terms, such as  
30 "alkoxycarbonyl", denotes  $-(C=O)-$ . The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted. The terms "carboxy" or  
35 "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $-CO_2H$ . The term "carboxyalkyl" embraces alkyl radicals substituted with

a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxy carbonyl" radicals with alkyl portions having 1 to 6 carbons. Examples of such lower alkoxy carbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "heterocyclalkyl" embraces saturated and partially unsaturated heterocyclic-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl

radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical.

5 The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals.

10 Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-

15 diethylamino or the like. The term "aryl amino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "aryl amino" radicals may be further substituted on the aryl ring portion of the radical. The term

20 "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one

25 alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The term "aminocarbonyl" denotes an amide group of the formula  $-C(=O)NH_2$ . The term

30 "alkylaminocarbonyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-

35 alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "alkylaminoalkyl" embraces radicals having one

or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term

5 "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective 10 amount of a 5-lipoxygenase inhibitor and of a cyclooxygenase-2 inhibitor compound in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of 15 treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having or susceptible to such inflammation or disorder a therapeutically-effective amount of a 5-lipoxygenase inhibitor and of a 20 cyclooxygenase-2 inhibitor compound. The method of the present invention also includes prophylactic or chronic treatment, especially in the case of arthritis and other inflammatory conditions which can lead to deterioration in the joints.

25 Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The 30 nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are 35 hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic,

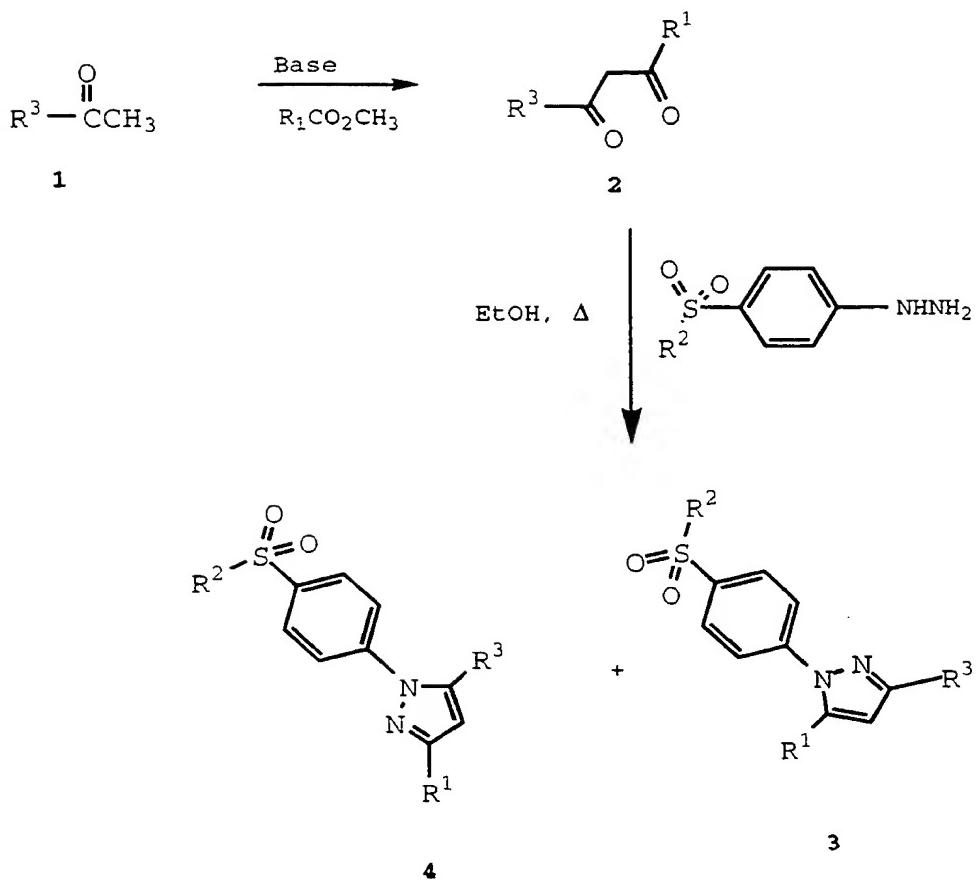
aromatic, araliphatic, heterocyclyl, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, 5 maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, 10 stearic, cyclohexylaminosulfonic, algenic,  $\beta$ -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, 15 magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding 20 compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

#### GENERAL SYNTHETIC PROCEDURES

25 The cyclooxygenase-2 inhibitor compounds of the invention can be synthesized according to the following procedures of Schemes I-X, wherein the R<sup>1</sup>-R<sup>3</sup> substituents are as defined for Formula I, above, except where further noted.

30

# Scheme I



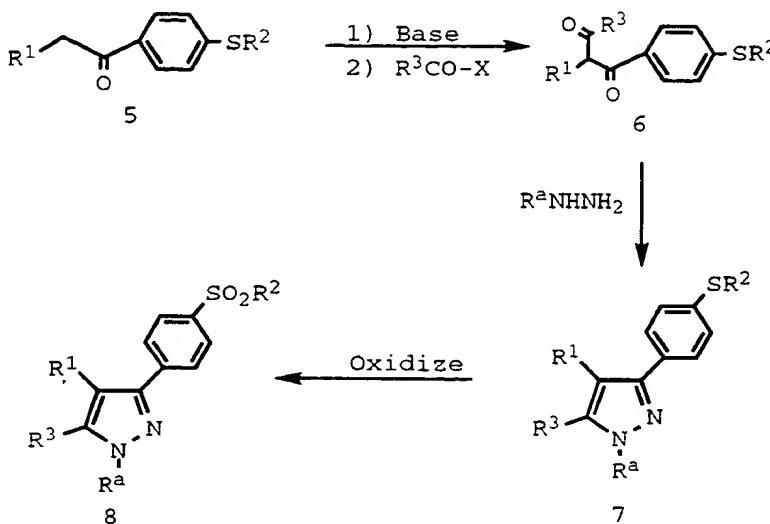
Synthetic Scheme I shows the preparation of

cyclooxygenase-2 inhibitor compounds, as described in U.S. patent No. 5,466,823, embraced by Formula I where R is Ar or Z (as defined in Scheme I), and R<sup>a</sup> is a radical defined above for the substituents optionally substituted on A. In step 1, ketone 1 is treated with a base, preferably NaOMe or NaH, and an ester, or ester equivalent, to form the intermediate diketone 2 (in the enol form) which is used without further purification. In step 2, diketone 2 in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the free base of a substituted hydrazine at reflux to afford a mixture of pyrazoles 3 and 4. Recrystallization or chromatography affords 3 usually

as a solid. Similar pyrazoles can be prepared by methods described in U.S. Pat. Nos. 4,146,721, 5,051,518, 5,134,142 and 4,914,121.

5

## Scheme II



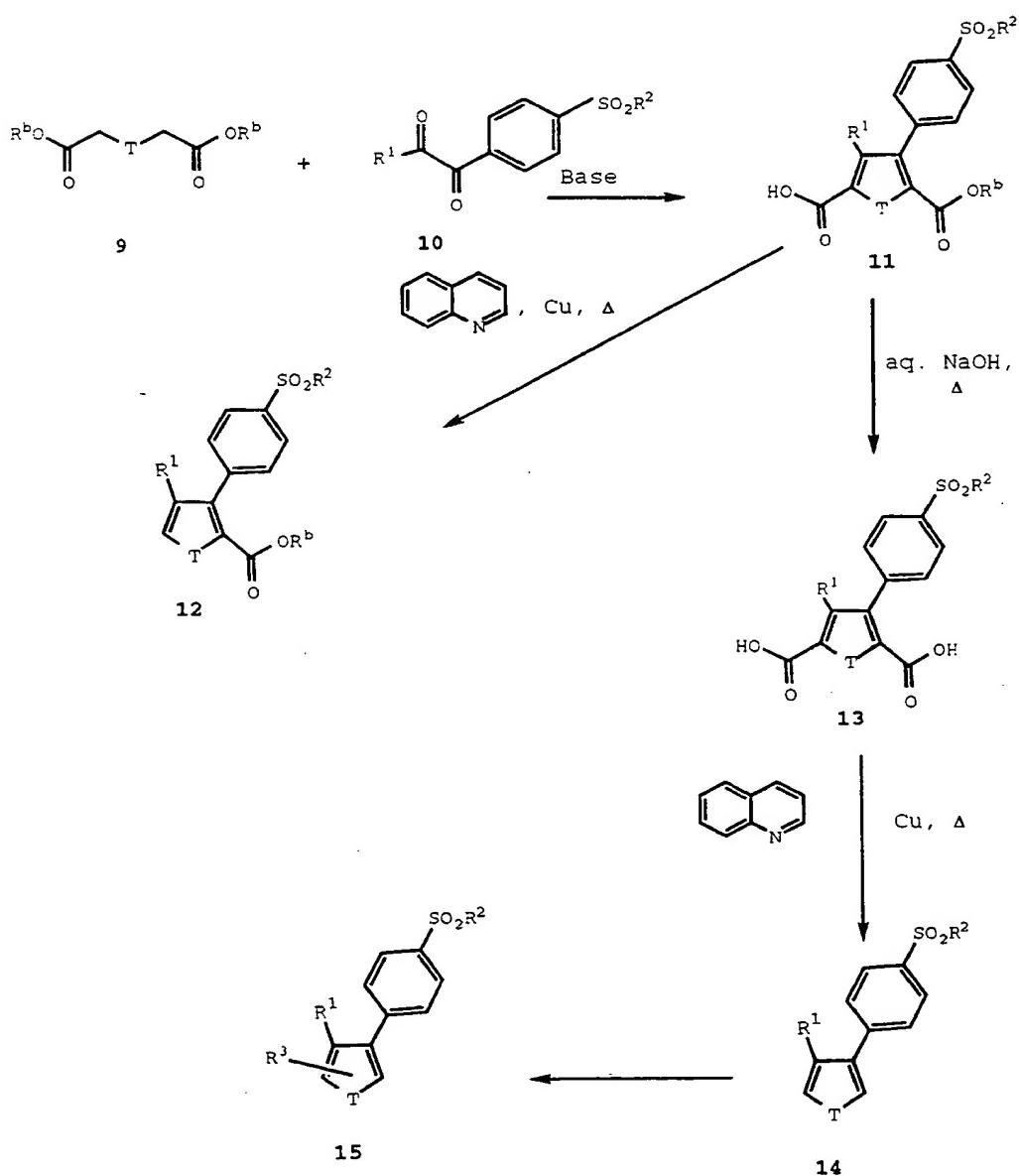
Scheme II shows the four step procedure for

- 10 forming cyclooxygenase-2 inhibitor pyrazoles **8** as described in U.S. patent No. 5,486,534 (where R<sup>a</sup> is alkyl) from ketones **5**. In step 1, ketone **5** is reacted with a base, such as lithium bis(trimethylsilyl)amide or lithium diisopropylamide (LDA) to form the anion.
- 15 In step 2, the anion is reacted with an acetylating reagent to provide diketone **6**. In step 3, the reaction of diketone **6** with hydrazine or a substituted hydrazine, gives pyrazole **7**. In step 4, the pyrazole **7** is oxidized with an oxidizing reagent, such as
- 20 Oxone® (potassium peroxymonosulfate), 3-chloroperbenzoic acid (MCPBA) or hydrogen peroxide, to give a mixture of the desired 3-(alkylsulfonyl)phenyl-pyrazole **8** and the 5-(alkylsulfonyl)phenyl-pyrazole isomer. The desired pyrazole **8**, usually a white or
- 25 pale yellow solid, is obtained in pure form either by chromatography or recrystallization.

Alternatively, diketone **6** can be formed from ketone **5** by treatment with a base, such as sodium hydride, in a solvent, such as dimethylformamide, and further reacting with a nitrile to form an  
 5 aminoketone. Treatment of the aminoketone with acid forms the diketone **6**. Similar pyrazoles can be prepared by methods described in U.S. Pat. No. 3,984,431.

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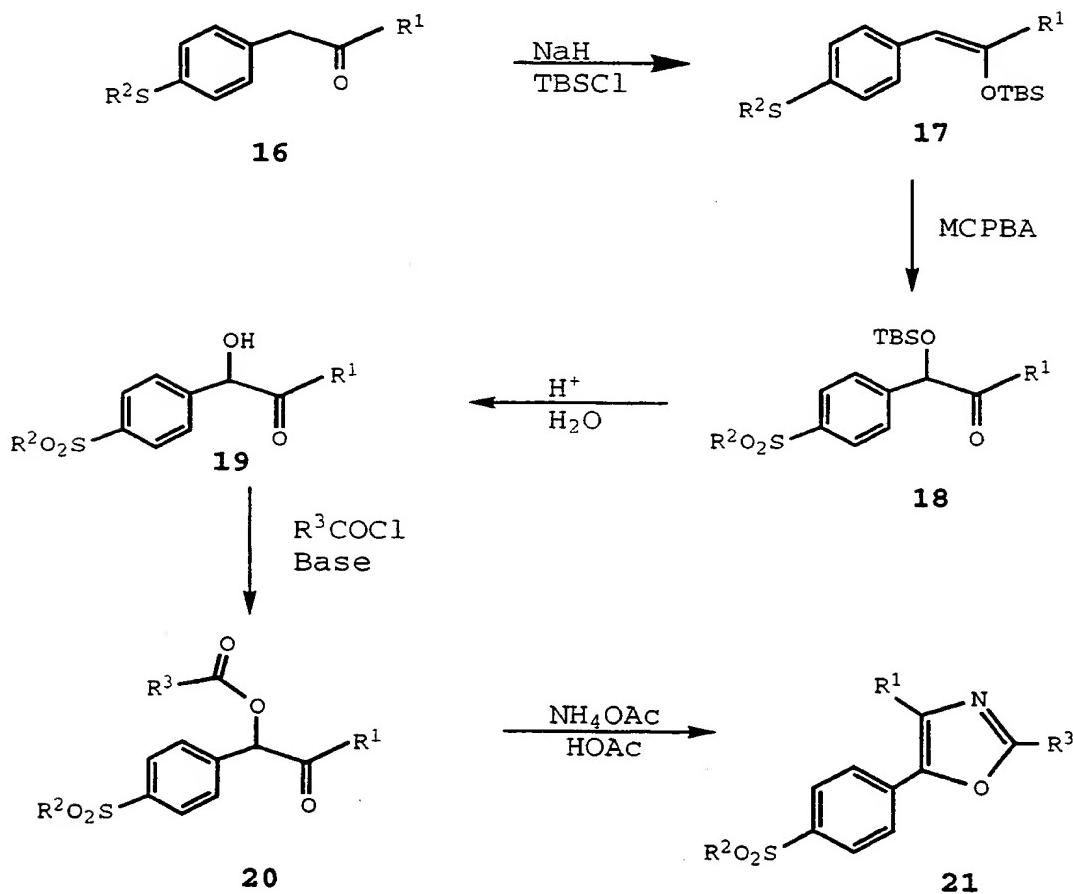
### Scheme III



Cyclooxygenase-2 inhibitor diaryl/heteroaryl thiophenes (where T is S, and R<sup>b</sup> is alkyl) can be prepared by the methods described in U.S. Patent Nos. 4,427,693, 4,302,461, 4,381,311, 4,590,205, and 5 4,820,827, and PCT documents WO 95/00501 and WO94/15932. Similar pyrroles (where T is N), furanones and furans (where T is O) can be prepared by methods described in PCT documents WO 95/00501 and WO94/15932.

10

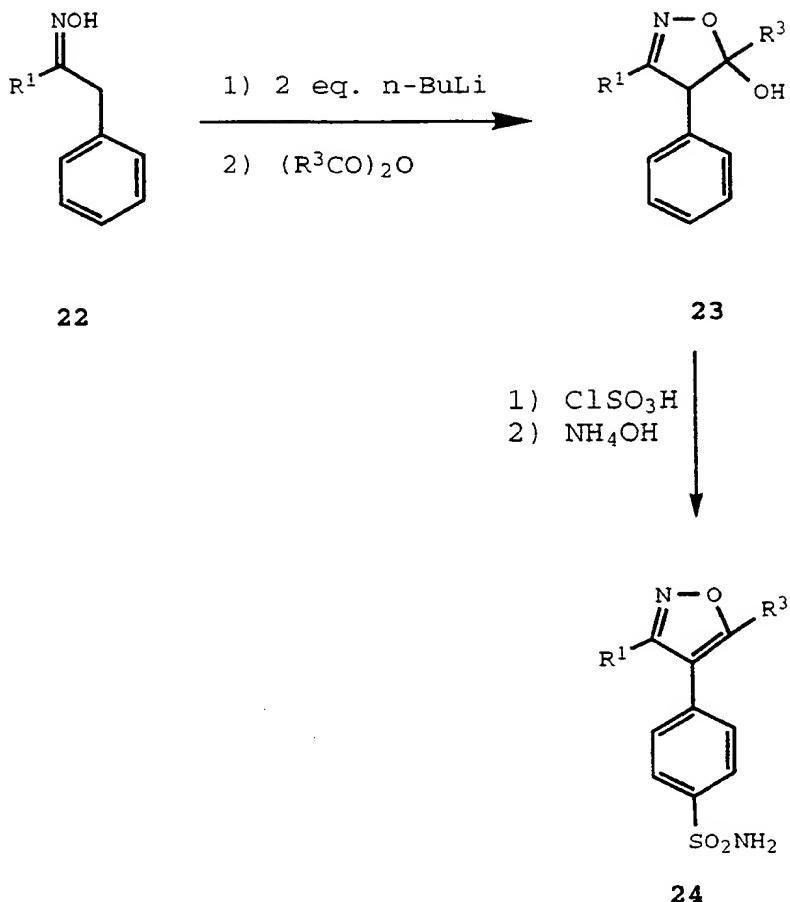
### Scheme IV



15

Cyclooxygenase-2 inhibitor diaryl/heteroaryl oxazoles can be prepared by the methods described in U.S. Patent Nos. 3,743,656, 3,644,499 and 3,647,858, and PCT documents WO 95/00501 and WO94/27980.

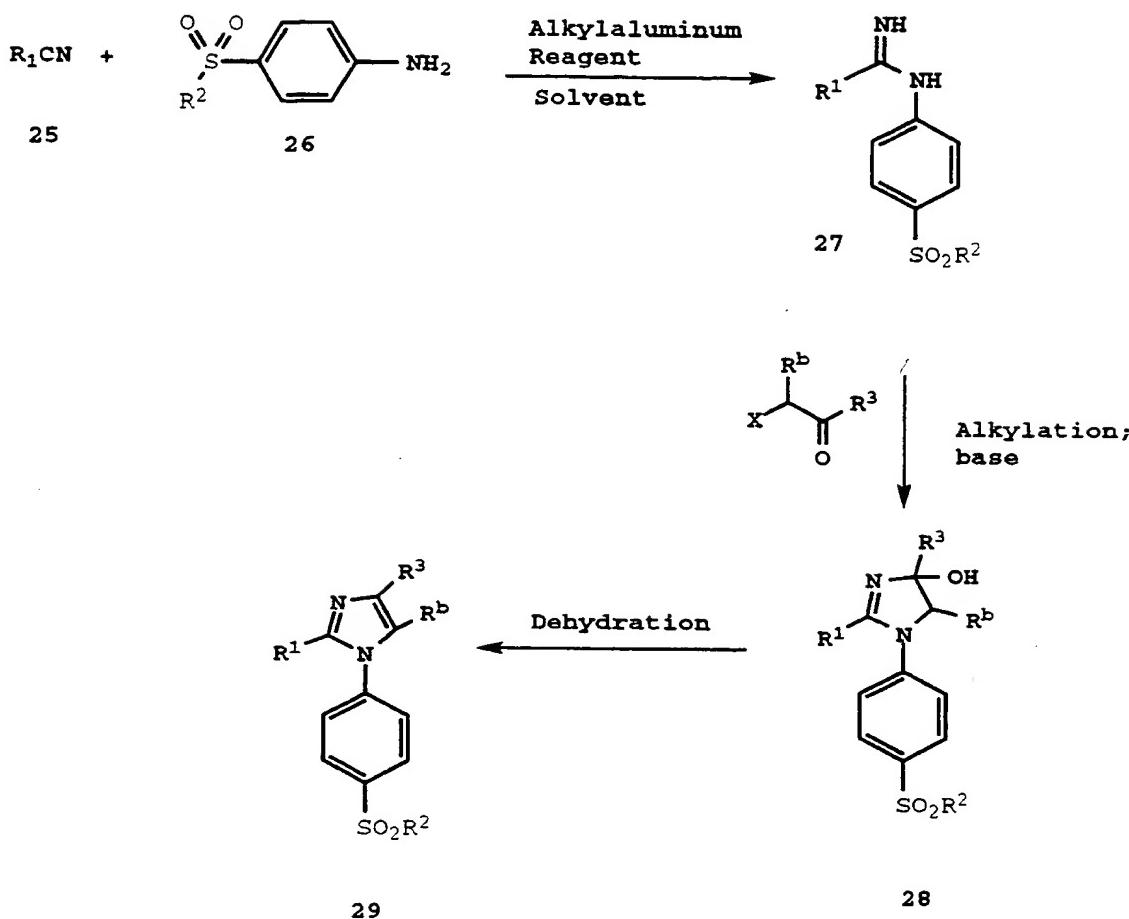
## Scheme V



5

Cyclooxygenase-2 inhibitor diaryl/heteroaryl isoxazoles can be prepared by the methods described in PCT documents WO92/05162, and WO92/19604, and European Publication EP 26928. Sulfonamides **24** can be formed from the hydrated isoxazole **23** in a two step procedure. First, hydrated isoxazole **23** is treated at about 0 °C with two or three equivalents of chlorosulfonic acid to form the corresponding sulfonyl chloride. In step two, the sulfonyl chloride thus formed is treated with concentrated ammonia to provide the sulfonamide derivative **24**.

## Scheme VI



Scheme VI shows the three step preparation of the cyclooxygenase-2 inhibitor imidazoles 29 of the present invention. In step 1, the reaction of substituted nitriles ( $R^1CN$ ) 25 with primary phenylamines 26 in the presence of alkylaluminum reagents such as trimethylaluminum, triethylaluminum, dimethylaluminum chloride, diethylaluminum chloride in the presence of inert solvents such as toluene, benzene, and xylene, gives amidines 27. In step 2, the reaction of amidine 27 with 2-haloketones (where  $X$  is Br or Cl) in the presence of bases, such as sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate or hindered tertiary amines such as *N,N'*-diisopropylethylamine, gives the 4,5-

dihydroimidazoles **28** (where R<sup>b</sup> is alkyl). Some of the suitable solvents for this reaction are isopropanol, acetone and dimethylformamide. The reaction may be carried out at temperatures of about 20°C to about

5 90°C. In step 3, the 4,5-dihydroimidazoles **28** may be dehydrated in the presence of an acid catalyst such as 4-toluenesulfonic acid or mineral acids to form the 1,2-disubstituted imidazoles **29** of the invention.

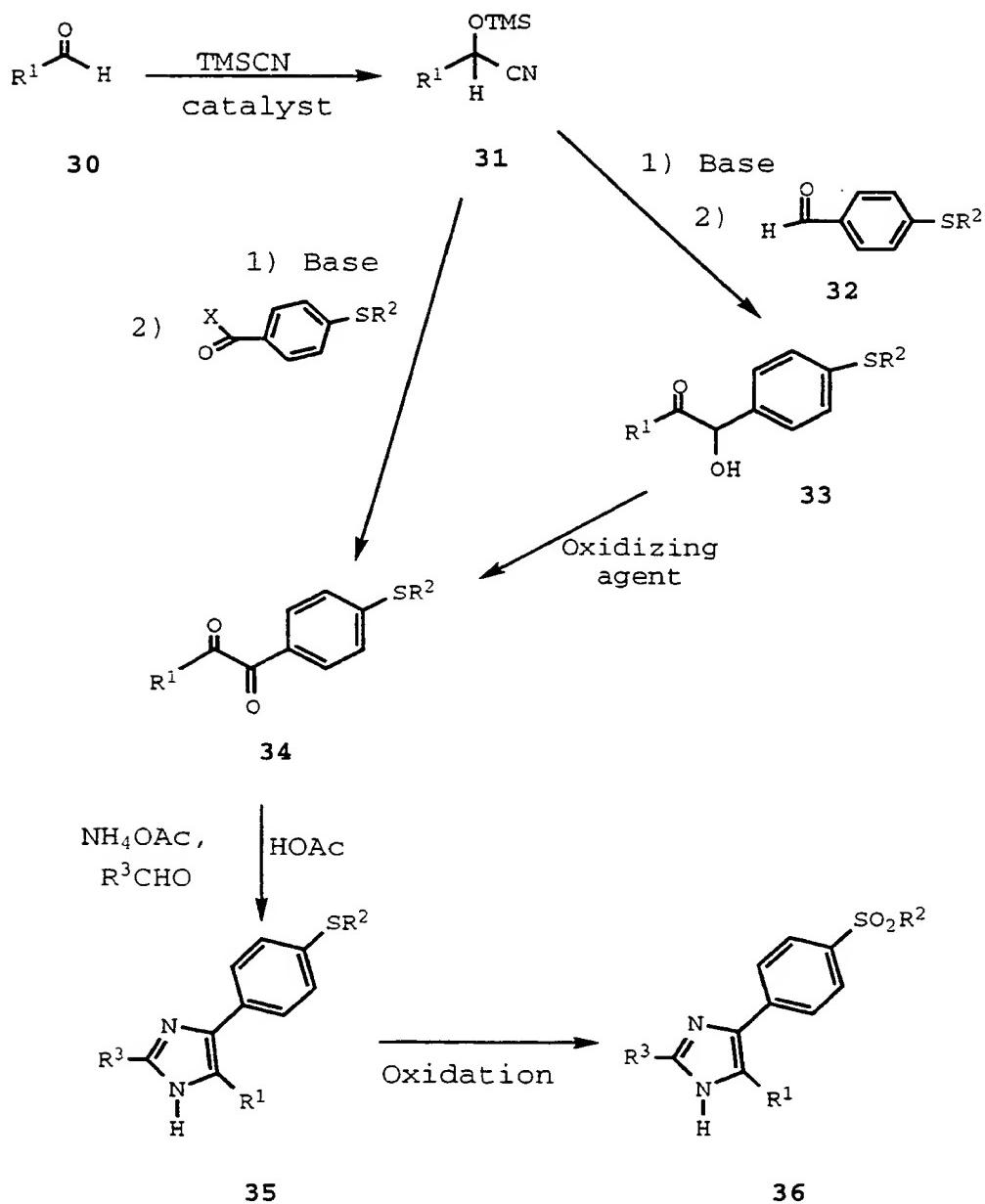
10 Suitable solvents for this dehydration step are e.g., toluene, xylene and benzene. Trifluoroacetic acid can be used as solvent and catalyst for this dehydration step.

15 In some cases (e.g., where YR = methyl or phenyl) the intermediate **28** may not be readily isolable. The reaction, under the conditions described above, proceeds to give the targeted imidazoles directly.

Similarly, imidazoles can be prepared having the sulfonylphenyl moiety attached at position 2 and R<sup>1</sup> attached at the nitrogen atom at position 1.

20 Diaryl/heteroaryl imidazoles can be prepared by the methods described in U.S. Patent Nos. 4,822,805, PCT document WO 96/03388 and PCT document WO 93/14082.

## Scheme VII



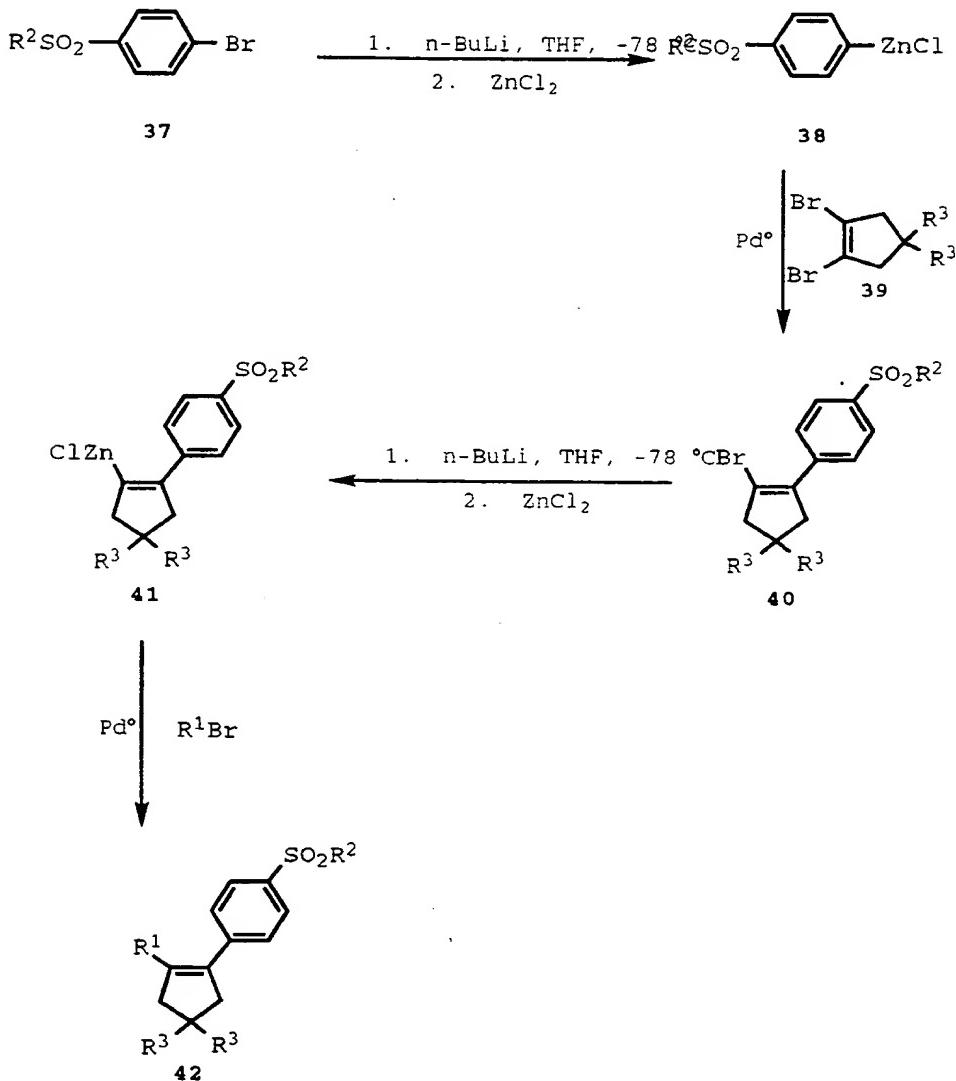
5       The subject imidazole cyclooxygenase-2 inhibitor  
compounds **36** of this invention may be synthesized  
according to the sequence outlined in Scheme VII.  
Aldehyde **30** may be converted to the protected  
cyanohydrin **31** by reaction with a trialkylsilyl  
10      cyanide, such as trimethylsilyl cyanide (TMSCN) in the

presence of a catalyst such as zinc iodide ( $ZnI_2$ ) or potassium cyanide (KCN). Reaction of cyanohydrin **31** with a strong base followed by treatment with benzaldehyde **32** (where  $R^2$  is alkyl) and using both acid and base treatments, in that order, on workup gives benzoin **33**. Examples of strong bases suitable for this reaction are lithium diisopropylamide (LDA) and lithium hexamethyldisilazane. Benzoin **33** may be converted to benzil **34** by reaction with a suitable oxidizing agent, such as bismuth oxide or manganese dioxide, or by a Swern oxidation using dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride.

Benzil **34** may be obtained directly by reaction of the anion of cyanohydrin **31** with a substituted benzoic acid halide. Any of compounds **33** and **34** may be used as intermediates for conversion to imidazoles **35** (where  $R^2$  is alkyl) according to chemical procedures known by those skilled in the art and described by M. R. Grimmett, "Advances in Imidazole Chemistry" in **Advances in Heterocyclic Chemistry**, 12, 104 (1970). The conversion of **34** to imidazoles **35** is carried out by reaction with ammonium acetate and an appropriate aldehyde (RYCHO) in acetic acid. Benzoin **36** may be converted to imidazoles **38** by reaction with formamide. In addition, benzoin **36** may be converted to imidazoles by first acylating with an appropriate acyl group (RYCO-) and then treating with ammonium hydroxide. Those skilled in the art will recognize that the oxidation of the sulfide (where  $R^2$  is methyl) to the sulfone may be carried out at any point along the way beginning with compounds **35**, and including oxidation of imidazoles **38**, using, for examples, reagents such as hydrogen peroxide in acetic acid, *m*-chloroperoxybenzoic acid (MCPBA) and potassium peroxymonosulfate (OXONE®).

Diaryl/heteroaryl imidazoles can be prepared by the methods described in U.S. Patent Nos. 3,707,475, 4,686,231, 4,503,065, 4,472,422, 4,372,964, 4,576,958, 3,901,908, PCT document WO 96/03387, 5 European publication EP 372,445, and PCT document WO 95/00501.

### Scheme VIII

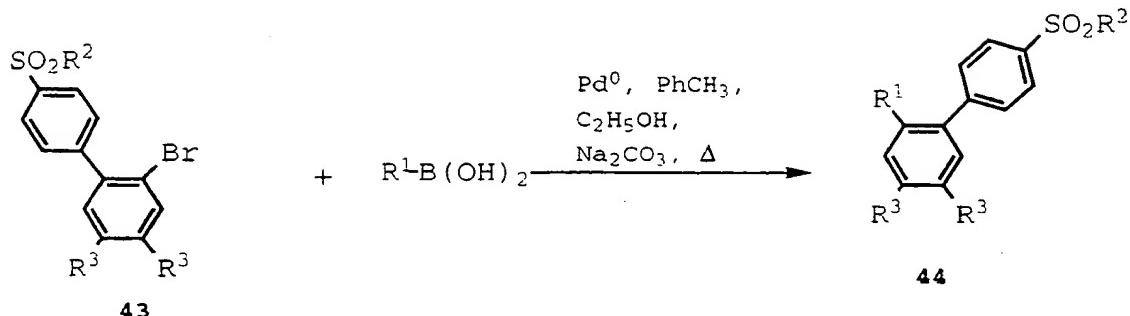


Diaryl/heteroaryl cyclopentene cyclooxygenase-2 inhibitors can be prepared by the methods described in

U.S. Patent No. 5,344,991, and PCT document WO 95/00501.

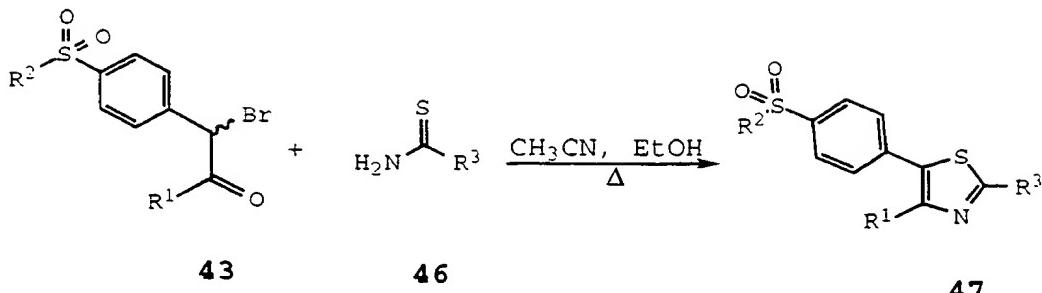
### Scheme IX

5



Similarly, Synthetic Scheme IX shows the procedure for the preparation of 1,2-diarylbenzene cyclooxygenase-2 inhibitor agents **44** from 2-bromo-biphenyl intermediates **43** (prepared similar to that described in Synthetic Scheme VIII) and the appropriate substituted phenylboronic acids. Using a coupling procedure similar to the one developed by Suzuki et al. [Synth. Commun., **11**, 513 (1981)], intermediates **43** are reacted with the boronic acids in toluene/ethanol at reflux in the presence of a  $\text{Pd}^0$  catalyst, e.g., tetrakis(triphenylphosphine) palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents **44** of this invention. Such terphenyl compounds can be prepared by the methods described by J. Li et al., [J. Med. Chem., **39**, 1846-56 (1996)].

## Scheme X



Diaryl/heteroaryl thiazole cyclooxygenase-2

5 inhibitors can be prepared by the methods described in U.S. Patent No. 4,051,250, 4,632,930, PCT document WO 96/03392, European Application EP 592,664, and PCT document WO 95/00501. Isothiazoles can be prepared as described in PCT document WO 95/00501.

10 Diaryl/heteroaryl pyridine cyclooxygenase-2 inhibitors can be prepared by the methods described in U.S. Patent Nos. 5,169,857, 4,011,328, 4,533,666, and WO96/10012.

15 Diaryl/heteroaryl benzofuran derivatives can be prepared by the methods described in WO96/06840.

The following examples contain detailed descriptions of the methods of preparation of combinations with compounds of Formula I. These detailed descriptions fall within the scope, and serve 20 to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and 25 temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

**BIOLOGICAL EVALUATION**

A combination therapy of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor was evaluated as described in the following tests.

5

**Example 1**

4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-  
1*H*-pyrazol-1-yl]benzenesulfonamide

10 Step 1: Preparation of 4,4,4-trifluoro-1-[4-(chlorophenyl)-butane-1,3-dione.

Ethyl trifluoroacetate (23.52 g, 166 mmol) was dissolved in methyl *tert*-butyl ether (75 mL). To the stirred solution was added 25 weight % sodium methoxide (40 mL, 177 mmol). Next 4'-chloroacetophenone (23.21 g, 150 mmol) was dissolved in methyl *tert*-butyl ether (20 mL), and added to the reaction dropwise. After stirring overnight (15.75 hours), 3N HCl (70 mL) was added. The organic layer was collected, washed with brine (75 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a 35.09 g of yellow-orange solid. The solid was recrystallized from isoctane to give 31.96 g (85%) of the dione: mp 66-67°C.

25 Step 2: Preparation of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide.

4-Sulphonamidophenyl hydrazine hydrochloride (982 mg, 4.4 mmol) was added to a stirred solution of 4,4,4-trifluoro-1-[4-chlorophenyl]-butane-1,3-dione (1.00 g, 4.0 mmol) in ethanol (50 mL). The reaction was heated to reflux and stirred for 20 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with water and brine and dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a light brown solid which was recrystallized from ethyl acetate and isoctane to give the pyrazole (1.28 g, 80%): mp 143-145°C. EI GC-MS M<sup>+</sup> = 401.

**Example 2**

4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

5   Step 1: Preparation of 3'-fluoro-4'-methoxy-acetophenone.

Acetyl chloride (51.0 g, 0.65 mol) was added dropwise to a stirred solution of aluminum chloride (80.0 g, 0.6 mol) and chloroform (750 mL), maintaining the temperature between 5-10°C. The mixture was stirred for 10 minutes at 5°C before 10 the dropwise addition of 2-fluoroanisole (62.6 g, 0.5 mol). The mixture was stirred at 0-10°C for 1 hour and poured into ice (1 L). The resultant layers were separated and the aqueous layer was extracted with dichloromethane (2x250 mL). The combined organic layers were washed with water (2x150 15 mL), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to a volume of 300 mL. Hexanes were added and a white solid formed which was isolated by filtration and air dried. This material was recrystallized from a mixture of dichloromethane and hexanes to afford (77.2 g, 92%) of 20 material suitable for use in the next step: mp 92-94°C.

Step 2: Preparation of 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione.

Ethyl difluoroacetate (4.06 g, 32.7 mmol) was dissolved 25 in methyl *tert*-butyl ether (50 mL). To the stirred solution was added 25 weight % sodium methoxide (7.07 g, 32.7 mmol) followed by 3'-fluoro-4'-methoxyacetophenone (5.0 g, 29.7 mmol). After stirring for 16 hours, 1N HCl (50 mL) was added. The organic layer was collected and washed with water (2x50 30 mL), dried over anhydrous MgSO<sub>4</sub>, filtered, and added to hexanes to precipitate a tan solid (7.0 g, 96%): mp 70-72°C.

Step 3: Preparation of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

35   4,4-Difluoro-1-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione from Step 2 (7.0 g, 28.4 mmol) was dissolved in ethanol (150 mL). To the stirred mixture was added 4-sulphonamidophenyl hydrazine hydrochloride (7.4 g, 33 mmol)

and stirred at reflux overnight (16 hours). The mixture was cooled and water was added until crystals slowly appeared. The product was isolated by filtration and air dried to provide the desired product as a light tan solid (9.8 g, 5 87%): mp 159-161°C. Anal. Calc'd. for C<sub>17</sub>H<sub>14</sub>N<sub>3</sub>SO<sub>3</sub>F<sub>3</sub>: C, 51.38; H, 3.55; N, 10.57. Found: C, 51.46; H, 3.52; N, 10.63.

#### Example 3

10 N' - [3 - [5 - (4 - Fluorophenoxy) furyl - 2 - yl] - 1 - methyl - 2 - propynyl] - N' - hydroxyurea

15 N' - [3 - [5 - (4 - Fluorophenoxy) furyl - 2 - yl] - 1 - methyl - 2 - propynyl] - N' - hydroxyurea was synthesized as described in WO document 92/01682: Anal. Calc'd. for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>F: C, 59.21, H, 4.31, N, 9.21. Found: C, 58.93, H, 4.32, N, 9.07.

#### Example 4

20 6 - [[3 - Fluoro - 5 - (3, 4, 5, 6 - tetrahydro - 4 - methoxy - 2H - pyran - 4 - yl) phenoxy] methyl] - 1 - methyl - 1H - quinolin - 2 - one

25 6 - [[3 - Fluoro - 5 - (3, 4, 5, 6 - tetrahydro - 4 - methoxy - 2H - pyran - 4 - yl) phenoxy] methyl] - 1 - methyl - 1H - quinolin - 2 - one was prepared as described by G. C. Crawley, et al. [J. Med. Chem., 35, 2600-2609 (1992)], EP 381,375, Hammer [J. Chem. Soc., 209 (1920)], and Balli and Schelz [Helv. Chim. Acta, 53, 1903 (1970)].

#### 30 Induction and assessment of collagen induced arthritis in mice

Arthritis was induced in 8-12 week old male DBA/1 mice by injection of 50 µg of chick type II collagen (CII) (provided by Dr. Marie Griffiths, Univ. of Utah, Salt Lake City, UT) in complete Freunds adjuvant (Sigma) on day 0 at the base of the tail as previously described [J. Stuart, Annual Rev. Immunol., 2, 199 (1984)]. Compounds were prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, MO), 0.025%

Tween 20 (Sigma). The cyclooxygenase-2 inhibitors (Example 1 and 2) and the 5-lipoxygenase inhibitors (Example 3 and 4) were administered alone or a cyclooxygenase-2 inhibitor and the 5-lipoxygenase 5 inhibitor in combination. The compounds were administered in non-arthritis animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55. Animals were boosted on day 21 with 50 µg 10 of collagen (CII) in incomplete Freunds adjuvant. The animals were subsequently evaluated several times each week for incidence and severity of arthritis until day 56. Any animal with paw redness or swelling was 15 counted as arthritic. Scoring of severity was carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as previously described [P. Wooley, et al., *Trans. Proc.*, 15, 180 (1983)]. The animals were measured for incidence of arthritis and severity in the 20 animals where arthritis was observed. The incidence of arthritis was determined at a gross level by observing the swelling or redness in the paw or digits. Severity was measured with the following guidelines. Briefly, 25 animals displaying four normal paws, i.e., no redness or swelling were scored 0. Any redness or swelling of digits or the paw were scored as 1. Gross swelling of the whole paw or deformity was scored as 2. Ankylosis of joints was scored as 3. Results are shown in Tables 1-2.

Table 1  
Incidence of collagen induced arthritis

|           | Ex. #1 <sup>a</sup><br>Example | Ex. #2 <sup>b</sup><br>Incidence (%) | Ex. #3 <sup>c</sup><br>Incidence (%) | Ex. #4 <sup>d</sup><br>Incidence (%) | Ex. #5 <sup>e</sup><br>Incidence (%) |
|-----------|--------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| Vehicle   | 100                            | 100                                  | 88                                   | 100                                  |                                      |
| 1 (COX-2) | 70                             |                                      |                                      | 67                                   |                                      |
| 2 (COX-2) |                                | 80                                   | 88                                   |                                      |                                      |
| 3 (5-LO)  | 100                            | 90                                   | 100                                  | 67                                   |                                      |
| 4 (5-LO)  |                                |                                      |                                      |                                      | 75                                   |
| COX-2+LO  |                                |                                      |                                      |                                      |                                      |
| 1+3       | 50                             |                                      |                                      | 7                                    |                                      |
| 2+3       |                                | 20                                   | 55                                   |                                      | 25                                   |
| 2+4       |                                |                                      |                                      |                                      | 30                                   |

Table 2  
Severity of collagen-induced arthritis

|           | Ex. #1 <sup>a</sup><br>Example | Ex. #2 <sup>b</sup><br>Severity | Ex. #3 <sup>c</sup><br>Severity | Ex. #4 <sup>d</sup><br>Severity | Ex. #5 <sup>e</sup><br>Severity |
|-----------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Vehicle   | 4.40±0.52                      | 4.22±0.52                       | 5.76±0.91                       | 4.42±0.59                       |                                 |
| 1 (COX-2) | 1.80±0.55                      |                                 |                                 | 1.58±0.40                       |                                 |
| 2 (COX-2) |                                | 3.00±0.73                       | 3.38±0.62                       |                                 |                                 |
| 3 (5-LO)  | 4.33±0.37                      | 3.30±0.73                       | 4.13±0.52                       | 1.50±0.35                       |                                 |
| 4 (5-LO)  |                                |                                 |                                 |                                 | 2.12±0.74                       |
| COX-2+LO  |                                |                                 |                                 |                                 |                                 |
| 1+3       | 0.50±0.17                      |                                 |                                 | 0.07                            |                                 |
| 2+3       |                                | 0.50±0.34                       | 1.78±.62                        |                                 | 0.63±0.42                       |
| 2+4       |                                |                                 |                                 |                                 | 0.3±0.15                        |

Dosing Ranges:

- 10 a - Example 1 @ 3 mpk/day; Example 3 @ 3 mpk/day;
- b - Example 2 @ 30 mpk/day; Example 3 @ 10 mpk/day;
- c - Example 2 @ 10 mpk/day; Example 3 @ 10 mpk/day;
- d - Example 1 M,W,F @ 10 mpk/day; Example 3 @ 10 mpk/day;
- 15 e - Example 2 @ 30 mpk/day; Example 3 @ 10 mpk/day;  
Example 4 @ 60 mpk/day;

Thus it can be seen that an ineffective amount of a 5-lipoxygenase inhibitor can effectively reduce the incidence and severity of inflammation when combined with varying doses of a cyclooxygenase-2 inhibitor.

**Example 5**

A formulation is prepared having the following components:

5        700 mg of a cyclooxygenase-2 inhibitor and 700 mg of a 5-lipoxygenase inhibitor.

**Example 6**

10      A formulation is prepared having the following components:

350 mg of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and 700 mg of N'-[{[5-(4-fluorophenoxy)furan-2-yl]-1-  
15      methyl-2-propynyl}-N'-hydroxyurea.

**Example 7**

20      A formulation is prepared having the following components:

350 mg of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and 700 mg of 6-{[3-fluoro-5-(3,4,5,6-tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy]methyl}-1-methyl-1H-  
25      quinolin-2-one .

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly,

intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a 5 tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also 10 be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds 15 that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the 20 particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily 25 dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.05 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

30 In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

35 For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in

a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or  
5 a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as  
10 propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other  
15 affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a  
20 patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact  
25 with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also  
30 function as the membrane. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an  
35 oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It

is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the 5 so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl 10 alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active 15 compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other 20 containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a 25 blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

30 Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients 35 are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

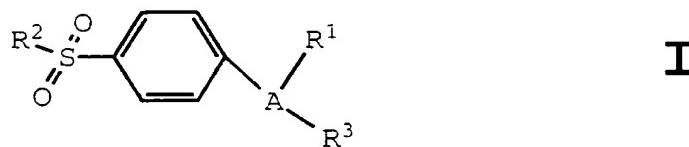
For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered 5 per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, 10 gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a 15 dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These 20 solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame 25 oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these 30 embodiments are not to be construed as limitations.

What is claimed is :

1. A combination comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor and a  
5 5-lipoxygenase inhibitor.

2. A combination comprising a therapeutically-effective amount of a 5-lipoxygenase inhibitor and a  
10 cyclooxygenase-2 inhibitor selected from Taisho NS-398,  
meloxicam, floculide, Merck MK-966, Merck L-752,860 and  
compounds of Formula I



15 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl,  
20 wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and  
25 alkylthio;

wherein R<sup>2</sup> is methyl or amino; and

wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio,  
30 alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl,  
35 aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl,

aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,  
N-arylamino carbonyl, N-alkyl-N-arylamino carbonyl,  
alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-  
arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-  
5 alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-  
arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-  
aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy,  
aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-  
10 arylaminosulfonyl, arylsulfonyl, N-alkyl-N-  
arylamino sulfonyl; or a pharmaceutically-acceptable  
salt thereof.

3. The combination of Claim 2 wherein the 5-  
15 lipoxygenase inhibitor is selected from masoprocol, tenidap,  
zileuton, Abbott A-76745, N'-[(5-(4-fluorophenoxy)furan-2-  
yl)-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-78773),  
(R)(+)-[(5-(4-fluorophenoxy)furan-2-yl)-1-methyl-2-  
propynyl]-N-hydroxyurea (Abbott A-79175), Abbott ABT 761,  
20 Dainippon AL-3264, Bayer Bay-x-1005, Biofor BF-389,  
bunaprolast, Ciba-Geigy CGS-25997, Cytomed CMI-392, Cytomed  
CMI-568, Atlantic Pharmaceutical CT3, Takeda CV-6504, Efamol  
EF-40, enazadrem phosphate, Leo Denmark ETH-615, flezelastine  
hydrochloride, flobufen, Merck Frosst L 663536, Merckle ML-  
25 3000, linazolast, lonapalene, Mercian MER W8020, N-hydroxy-N-[1-(2-phenyl-5-benzofuranyl)ethyl]urea (R. W. Johnson  
Research Institute), ontazolast, 3M Pharmaceuticals R-840,  
rilopirox, Hoechst Marion Roussel RU54808, Schering Plough  
SCH 40120, tepoxalin, Tanabe 757, Tanabe 799, Terumo TMK-688,  
30 Glaxo Wellcome WILD20, Zeneca ZD-2138, Abbott A-121798,  
Abbott A 72694, Abbott A-80263, Biofor BF-397, Bristol-Myers  
Squibb BU-4601A, carbazoycin C, lagunamycin, Wellcome BW-70C,  
Ciba-Geigy CGS-26529, Warner-Lambert CI 1004, Warner-Lambert  
PD-136005, Warner-Lambert PD-145246, Eisai E 3040, Fujirebio  
35 F-1322, Fisons FPL-64170, Fujisawa FR 110302, Nippon Hypox HX  
0386, Merck & Co L-699333, Merck Frosst L 739010, Lilly LY-  
269415, Lilly LY 178002, Meiji Milk MM-7002, Hoechst Roussel

P 8892, Hoechst Roussel P 8977, Hoechst Roussel HP977,  
SmithKline Beecham SB-202235, Green Cross SS-81-OH, Terumo  
Keio University TMK 685, American Home Products WAY-121520,  
American Home Products WAY-125007, Zeneca ZD 7717, Zeneca ZM-  
5 216800, Zeneca ZM 230487, 1,2-dihydro-n-(2-thiazolyl)-1-  
oxopyrrolo(3,2,1-kl)phenothiazine-1-carboxamide, Abbott A-  
65260, Abbott A-69412, Abbott Abbott-63162, American Home  
Products AHR-5333, Bayer Bay-q-1531, Boehringer Ingelheim BI-  
L-357, Boehringer Ingelheim BI-L-93BS, Boehringer Ingelheim  
10 BIL 226XX, Bristol-Myers Squibb BMY-30094, carbazomycin B,  
Wellcome BW 4C, Wellcome BW-B218C, Wellcome BW-B70C, Chauvin  
CBS-1114, Ciba-Geigy CGS-21595, Ciba-Geigy CGS-22745, Ciba-  
Geigy CGS-23885, Ciba-Geigy CGS 24891, Ciba-Geigy CGS-8515,  
Chiesi CHF-1909, Warner-Lambert CI-986, Warner-Lambert CI  
15 987, cirsiliol, docebenone, DuPont Merck DuP-654, Eisai E  
5110, Eisai E-6080, Green Cross EN-105, enofelast,  
epocarbazolin-A, eprovafen, evandamine, forsythiaside, Fisons  
FPL 62064, Glaxo GR-80907, Zeneca ICI-211965, isoflavans,  
Kyowa Hakko KF-8940, Merck & Co L-651392, Merck & Co L-  
20 651896, Merck & Co L-652343, Merck & Co L-656224, Merck & Co  
L-670630, Merck & Co L-674636, Merck & Co L-691816, Lilly LY-  
233569, Lilly LY-280810, Merck & Co MK-591, Merck & Co MK-  
886, nitrosoxacin-A, Ono ONO-5349, Ono ONO-LP-219, Ono ONO-  
LP-269, Warner-Lambert PD-127443, Purdue Frederick PF-5901,  
25 Sandoz QA-208-199, Johnson & Johnson R-68151, Johnson &  
Johnson R-85355, Rhone-Poulenc Rorer Rev-5367, Rhone-Poulenc  
Rorer RG-5901-A, Rhone-Poulenc Rorer RG-6866, Roussel-Uclaf  
RU-46057, Searle SC-41661A, Searle SC-45662, Sandoz SDZ-210-  
610, SmithKline Beecham SK&F-104351, SmithKline Beecham SK&F-  
30 104493, SmithKline Beecham SK&F-105809, Synthelabo SL-81-  
0433, Teijin TEI-8005, Terumo TMK-777, Terumo TMK-781, Terumo  
TMK-789, Terumo TMK-919, Terumo TMK-992, Teikoku Hormone TZI-  
2721, Teikoku Hormone TZI-41127, American Home Products WAY-  
120739, American Home Products WY 47288, American Home  
35 Products Wy-48252, American Home Products Wy-50295, and  
Yoshitomi Y-19432.

4. The combination of Claim 3 wherein the 5-lipoxygenase inhibitor is selected from ibudilast, masoprolol, tenidap, zileuton, Abbott A-121798, Abbott A-76745, N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-78773), (R)(+)-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-hydroxyurea (Abbott A-79175), Abbott ABT 761, Dainippon AL-3264, Bayer Bay-x-1005, Biofor BF-389, bunaprolast, Cytomed CMI-392, Cytomed CMI-568, Atlantic 10 Pharmaceutical CT3, Takeda CV-6504, Ciba-Geigy CGS-26529, Ciba-Geigy CGS-25997, enazadrem phosphate, Eisai E 3040, Leo Denmark ETH-615, flezelastine hydrochloride, flobufen, Fujirebio F-1322, Hoechst Roussel HP977, linazolast, lonapalene, Merck Frosst L 663536, Merck 15 Frosst L 699333, Merckle ML-3000, Mercian MER W8020, N-hydroxy-N-[1-(2-phenyl-5-benzofuranyl)ethyl]urea (R. W. Johnson Research Institute), ontazolast, Hoechst Roussel P 8892, Hoechst Roussel P 8977, Warner-Lambert PD-145246, Purdue Frederick PF-5901, 3M Pharmaceuticals R-20 840, rilopirox, Hoechst Marion Roussel RU54808, Schering Plough SCH 40120, Tanabe 757, Tanabe 799, tepoxalin, Terumo TMK-688, Scotia Pharmaceuticals EF-40, Glaxo Wellcome WILD20, Zeneca ZD 7717, and Zeneca ZD-2138.

25 5. The combination of Claim 4 wherein the 5-lipoxygenase inhibitor is selected from ibudilast, masoprolol, tenidap, zileuton, Abbott A-76745, N'-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N'-hydroxyurea (Abbott A-78773), (R)(+)-[[5-(4-fluorophenoxy)furan-2-yl]-1-methyl-2-propynyl]-N-30 hydroxyurea (Abbott A-79175), Abbott ABT 761, Bayer Bay-x-1005, Cytomed CMI-392, Ciba-Geigy CGS-26529, Biofor BF-389, Cytomed CMI-392, Eisai E 3040, Scotia Pharmaceuticals EF-40, Leo Denmark ETH-615, flobufen, 35 Fujirebio F-1322, linazolast, lonapalene, Merck Frosst L 699333, Merckle ML-3000, ontazolast, Purdue Frederick

PF-5901, 3M Pharmaceuticals R-840, rilopirox, Terumo TMK-688, and Zeneca ZD-2138.

6. The combination of Claim 2 wherein A is selected  
5 from 5- or 6-member partially unsaturated heterocyclyl,  
5- or 6-member unsaturated heterocyclyl, 9- or 10-member  
unsaturated condensed heterocyclyl, lower cycloalkenyl  
and phenyl; wherein R<sup>1</sup> is selected from 5- and 6-  
membered heterocyclyl, lower cycloalkyl, lower  
10 cycloalkenyl and aryl selected from phenyl, biphenyl and  
naphthyl, wherein R<sup>1</sup> is optionally substituted at a  
substitutable position with one or more radicals  
selected from lower alkyl, lower haloalkyl, cyano,  
carboxyl, lower alkoxy carbonyl, hydroxyl, lower  
15 hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino,  
phenylamino, lower alkoxyalkyl, lower alkylsulfinyl,  
halo, lower alkoxy and lower alkylthio; wherein R<sup>2</sup> is  
methyl or amino; and wherein R<sup>3</sup> is a radical selected  
from hydrido, oxo, cyano, carboxyl, lower  
20 alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl,  
halo, lower alkyl, lower alkyloxy, lower cycloalkyl,  
phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl,  
lower hydroxylalkyl, lower aralkyl, acyl,  
phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered  
25 heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl,  
lower alkylamino, lower aminoalkyl, lower  
alkylaminoalkyl, phenoxy, and lower aralkoxy; or a  
pharmaceutically-acceptable salt thereof.

30 7. The combination of Claim 6 wherein A is  
selected from oxazolyl, isoxazolyl, thienyl, furyl,  
dihydrofuryl, pyrrolyl, pyrazolyl, thiazolyl, phenyl,  
imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl,  
cyclopentadienyl, and pyridyl; wherein R<sup>1</sup> is selected  
35 from pyridyl optionally substituted at a substitutable  
position with one or more methyl radicals, and phenyl  
optionally substituted at a substitutable position with

one or more radicals selected from methyl, ethyl,  
isopropyl, butyl, *tert*-butyl, isobutyl, pentyl, hexyl,  
fluoromethyl, difluoromethyl, trifluoromethyl, cyano,  
carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxyl,  
5 hydroxymethyl, trifluoromethoxy, amino, N-methylamino,  
N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-  
butylamino, N-methyl-N-ethylamino, phenylamino,  
methoxymethyl, methylsulfinyl, fluoro, chloro, bromo,  
methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and  
10 methylthio; wherein R<sup>2</sup> is methyl or amino; and wherein  
R<sup>3</sup> is a radical selected from hydrido, oxo, cyano,  
carboxyl, methoxycarbonyl, ethoxycarbonyl,  
carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl,  
fluoro, chloro, bromo, methyl, ethyl, isopropyl, butyl,  
15 *tert*-butyl, isobutyl, pentyl, hexyl, difluoromethyl,  
trifluoromethyl, pentafluoroethyl, heptafluoropropyl,  
difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy,  
n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl,  
thiazolyl, oxazolyl, furyl, pyrazinyl, hydroxymethyl,  
20 hydroxylpropyl, benzyl, formyl, phenylcarbonyl,  
methoxymethyl, furylmethoxy, aminocarbonyl, N-  
methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-  
dimethylamino, N-ethylamino, N,N-dipropylamino, N-  
butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-  
25 dimethylaminomethyl, N-methyl-N-ethylaminomethyl,  
benzyloxy, and phenoxy; or a pharmaceutically-  
acceptable salt thereof.

8. The combination of Claim 7 selected from  
30 compounds, and their pharmaceutically-acceptable salts,  
of the group consisting of

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-  
(trifluoromethyl)pyrazole;  
35 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-  
3-(trifluoromethyl)pyrazole;

4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-  
yl)benzenesulfonamide  
4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-  
yl)benzenesulfonamide;  
5 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-  
yl)benzenesulfonamide;  
4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-  
yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-  
10 yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-  
yl)benzenesulfonamide;  
4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-  
15 yl)benzenesulfonamide;  
4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-  
yl)benzenesulfonamide  
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
yl]benzenesulfonamide;  
4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-  
20 yl]benzenesulfonamide;  
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
yl]benzenesulfonamide;  
4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
25 yl]benzenesulfonamide;  
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-  
yl]benzenesulfonamide;  
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-  
30 yl]benzenesulfonamide;  
4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-  
pyrazol-1-yl]benzenesulfonamide;  
4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-  
35 yl]benzenesulfonamide;  
4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-  
yl]benzenesulfonamide;

- 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-15 15-yl]benzenesulfonamide;
- 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 20 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 25 25 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 30 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-
- 35 trifluoromethylthiazole;
- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
- 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
- 5 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
- 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- 10 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
- 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- 15 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
- 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-20 pyridine-3-carbonitrile;
- 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
- 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 25 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 3-[(1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-30 imidazol-2-yl]pyridine;
- 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 35 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

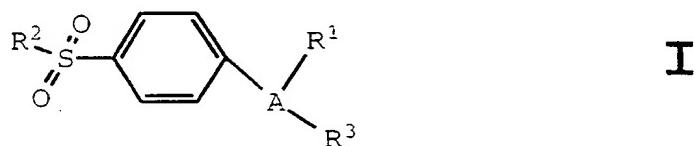
- 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 5 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-10 1H-imidazole;
- 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 15 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 20 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 25 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- 30 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 35 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

- 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;  
4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;  
5 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;  
ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;  
4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;  
10 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;  
1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;  
15 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;  
4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;  
5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-  
20 6-(trifluoromethyl)pyridine;  
2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;  
5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynloxy)-6-(trifluoromethyl)pyridine;  
25 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;  
4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
30 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;  
4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;  
4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
35 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;  
4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

- 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 5 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 10 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 15 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-  
20 yl]benzenesulfonamide;
- 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 25 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-  
y1]benzenesulfonamide;
- 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(  
30 methylsulfonyl)benzene;
- 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-  
y1]benzenesulfonamide;
- 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-  
y1]benzenesulfonamide;
- 35 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)  
phenyl]oxazol-2-yl]-2-benzyl-acetate;

2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;  
 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;  
 5 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;  
 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and  
 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-  
 10 oxazolyl]benzenesulfonamide.

9. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a 5-lipoxygenase inhibitor and a cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



20 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R<sup>1</sup> is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R<sup>2</sup> is methyl or amino; and

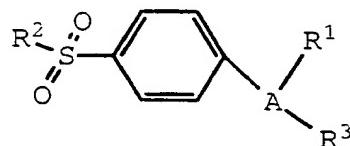
wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl,

cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio,  
 alkylcarbonyl, cycloalkyl, aryl, haloalkyl,  
 heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl,  
 acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl,  
 5      arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl,  
 arylthioalkyl, aryloxyalkyl, aralkylthioalkyl,  
 aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl,  
 aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,  
 N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl,  
 10     alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-  
 arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-  
 alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-  
 arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-  
 15     aralkylaminoalkyl, N-alkyl-N-aryl aminoalkyl, aryloxy,  
 aralkoxy, arylthio, aralkylthio, alkylsulfinyl,  
 alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-  
 arylaminosulfonyl, arylsulfonyl, N-alkyl-N-  
 arylaminosulfonyl; or a pharmaceutically-acceptable  
 salt thereof.

20

10. A method of treating inflammation or an  
 inflammation-associated disorder in a subject, said  
 method comprising co-administering to the subject having  
 or susceptible to such inflammation or inflammation-  
 25     associated disorder, a therapeutically-effective amount  
 of a 5-lipoxygenase inhibitor and a cyclooxygenase-2  
 inhibitor selected from Taisho NS-398, meloxicam,  
 floculide, Merck MK-966, Merck L-752,860 and compounds  
 of Formula I

30



I

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R<sup>1</sup> is at least one substituent selected

5 from heterocyclyl, cycloalkyl, cycloalkenyl and aryl,  
wherein R<sup>1</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, 10 nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R<sup>2</sup> is methyl or amino; and

wherein R<sup>3</sup> is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, 15 cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, 20 arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N- 25 arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N- aralkylaminoalkyl, N-alkyl-N-arylaminooalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, 30 alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N- arylaminosulfonyl; or a pharmaceutically-acceptable salt thereof.

35 11. The method of Claim 10 wherein said 5-lipoxygenase inhibitor and said cyclooxygenase-2 inhibitor are administered in a sequential manner.

12. The method of Claim 10 wherein said 5-lipoxygenase inhibitor and said cyclooxygenase-2 inhibitor are administered in a substantially simultaneous manner.

5 13. The method of Claim 10 wherein the 5-lipoxygenase inhibitor is selected from compounds of Claim 4.

10 14. The method of Claim 13 wherein the 5-lipoxygenase inhibitor is selected from compounds of Claim 5.

15 15. The method of Claim 10 wherein the cyclooxygenase-2 inhibitor is selected from compounds of Claim 6, or a pharmaceutically-acceptable salt thereof.

16 16. The method of Claim 15 wherein the cyclooxygenase-2 inhibitor is selected from compounds of Claim 7, or a pharmaceutically-acceptable salt thereof

17. The method of Claim 16 wherein the cyclooxygenase-2 inhibitor is selected from compounds of Claim 8, or a pharmaceutically-acceptable salt thereof

20 18. The method of Claim 10 wherein the condition is inflammation.

19. The method of Claim 10 wherein the condition is an inflammation-associated disorder.

25 20. The method of Claim 19 wherein the inflammation-associated disorder is arthritis.

21. The method of Claim 10 wherein the subject is susceptible to inflammation.

22. The method of Claim 10 wherein the subject is susceptible to an inflammation-associated disorder.

30 23. The method of Claim 22 wherein the subject is susceptible to arthritis.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/10106

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A61K31/00 A61K31/10 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| P,X        | <p>WO,A,96 03387 (G.D.SEARLE &amp; CO.) 8<br/>         February 1996<br/>         cited in the application<br/>         see page 1, line 1 - page 2, line 12<br/>         see page 6, line 32 - page 8, line 2<br/>         see page 8, line 3 - line 7<br/>         see page 8, line 22 - line 25<br/>         see claims 1-28<br/>         see page 197, line 24 - page 201, line 29<br/>         ---<br/>         -/-</p> | 1-23                  |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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1

Date of the actual completion of the international search

11 November 1996

Date of mailing of the international search report

29.11.96

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Economou, D

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/10106

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
|--|--|-----------------------|
| Category   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| P,X  | <p>WO,A,96 03388 (G.D.SEARLE &amp; CO.) 8 February 1996<br/>           cited in the application<br/>           see page 1, line 1 - page 2, line 12<br/>           see page 4, line 28 - page 5, line 37<br/>           see page 6, line 1 - line 5<br/>           see page 6, line 20 - line 23<br/>           see page 212, line 4 - page 215, line 33<br/>           see claims 1-48</p> <p>---</p> | 1-23                  |
| X  | <p>EXPERT OPINION ON INVESTIGATIONAL DRUGS,<br/>           vol. 4, no. 3, March 1995,<br/>           pages 243-249, XP000603398<br/>           HUANG P., ET AL.: "CYCLOOXYGENASE AND<br/>           5-LIPOOXYGENASE INHIBITORS FOR THE<br/>           PREVENTION AND TREATMENT OF CANCER"<br/>           see page 243, left-hand column, line 1 -<br/>           line 14</p> <p>---</p>                | 1                     |
| Y  | <p>US,A,5 098 932 (HAMON) 24 March 1992<br/>           cited in the application<br/>           see right-hand column, line 39 - line 58<br/>           see claims 1-9</p> <p>---</p>   | 1-23                  |
| Y  | <p>WO,A,94 26731 (MERCK FROSST CANADA INC.)<br/>           24 November 1994<br/>           cited in the application<br/>           see page 1, line 1 - page 2, paragraph 1<br/>           see page 6, line 5 - page 9, line 6<br/>           see page 9, line 24 - page 13, line 30<br/>           see claims 1-23</p> <p>---</p>   | 1-23                  |
| Y  | <p>WO,A,94 15932 (SEARLE G.D. &amp; CO) 21 July<br/>           1994<br/>           cited in the application<br/>           see page 1, line 15 - page 2, line 29<br/>           see page 7, line 11 - page 8, line 31<br/>           see page 72, line 23 - page 75, line 31<br/>           see claims 1-34</p> <p>---</p>   | 1-23                  |
| Y  | <p>WO,A,94 13635 (MERCK FROSST CANADA INC.)<br/>           23 June 1994<br/>           cited in the application<br/>           see page 1, line 9 - page 2, line 11<br/>           see page 12, line 24 - page 19, line 27<br/>           see claims 1-30</p> <p>---</p>   | 1-23                  |
| Y  | <p>WO,A,95 15316 (SEARLE G.D. &amp; CO) 8 June<br/>           1995<br/>           cited in the application<br/>           see page 1, line 13 - line 38<br/>           see page 7, line 8 - page 8, line 16<br/>           see page 181, line 26 - page 183, line 21<br/>           see claims 1-59</p> <p>---</p>   | 1-23                  |
| 1  |  | -/-                   |

**INTERNATIONAL SEARCH REPORT**

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|---|
| International Application No<br>PCT/US 96/10106 |
|---|

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|----------|--|-----------------------|
| P,Y      | US,A,5 510 368 (LAU ET AL.) 23 April 1996<br>cited in the application<br>see column 1, line 5 - line 48<br>see column 4, line 10 - column 7, line 4<br>see claims 1-9<br>---   | 1-23                  |
| P,X      | US,A,5 476 944 (PARTIS ET AL.) 19 December 1995  | 1                     |
| P,Y      | see column 1, line 14 - line 22<br>see column 1, line 33 - line 41<br>see column 2, line 50 - line 61<br>see column 4, line 5 - line 9<br>see column 7, line 54 - column 8, line 47<br>see column 8, line 50 - column 10, line 67<br>see column 11, line 28 - column 21, line 48<br>see column 31, line 31 - column 34, line 22<br>see table 1<br>see claims 1-23<br>--- | 1-23                  |
| Y        | WO,A,94 20480 (MERCK FROSST CANADA INC.) 15 September 1994<br>cited in the application<br>see page 1, line 5 - page 2, line 7<br>see page 8, line 28 - page 14, line 22<br>see claims 1-23<br>---  | 1-23                  |
| Y        | US,A,5 356 898 (BELLIOTTI ET AL.) 18 October 1994<br>cited in the application<br>see abstract<br>see column 1, line 14 - line 39<br>see column 3, line 55 - column 4, line 25<br>see column 9, line 37 - line 54<br>see claims 1-25<br>---   | 1-23                  |
| Y        | US,A,5 298 521 (FERRERO) 29 March 1994<br>cited in the application<br>see column 1, line 16 - line 20<br>see column 7, line 64 - column 8, line 53<br>see claims 1-11<br>---   | 1-23                  |
| Y        | US,A,5 242 940 (WACHTER ET AL.) 7 September 1993<br>cited in the application<br>see column 1, line 13 - line 20<br>see column 3, line 34 - line 40<br>see column 4, line 16 - line 50<br>see column 8, line 49 - line 65<br>see claims 1-6<br>---  | 1-23                  |
|          |  | -/-                   |

**INTERNATIONAL SEARCH REPORT**

|   |
|---|
| International Application No<br>PCT/US 96/10106 |
|---|

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| Y          | US,A,5 234 950 (EDWARDS ET AL.) 10 August 1993<br>cited in the application<br>see column 1, line 4 - line 48<br>see column 18, line 33 - line 52<br>see claims 1-7<br>---<br>WO,A,95 00501 (MERCK FROSST CANADA INC.) 5 January 1995<br>cited in the application<br>see page 1, line 8 - page 2, line 7<br>see page 27, line 9 - page 32, line 25<br>see claims 1-32<br>---<br>WO,A,94 27980 (SEARLE G.D. & CO.) 8 December 1994<br>cited in the application<br>see page 1, line 30 - page 2, line 12<br>see page 6, line 13 - page 7, line 13<br>see page 104, line 25 - line 37<br>see claims 1-42<br>----- | 1-23                  |
| Y          |   | 1-23                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/10106

| Patent document cited in search report | Publication date | Patent family member(s)   |   | Publication date   |
|--|------------------|---|---|--|
| WO-A-9603387                           | 08-02-96         | AU-A-   | 3271695   | 22-02-96   |
| WO-A-9603388                           | 08-02-96         | AU-A-   | 3202595   | 22-02-96   |
| US-A-5098932                           | 24-03-92         | AU-B-<br>CA-A-<br>DE-D-<br>DE-T-<br>EP-A-<br>ES-T-<br>IE-B-<br>IL-A-<br>JP-A-<br>US-A-                            | 622965<br>2006095<br>68913940<br>68913940<br>0375457<br>2063149<br>63211<br>92580<br>3135976<br>5219881   | 30-04-92<br>23-06-90<br>21-04-94<br>14-07-94<br>27-06-90<br>01-01-95<br>05-04-95<br>12-04-94<br>10-06-91<br>15-06-93   |
| WO-A-9426731                           | 24-11-94         | AU-A-   | 6718494   | 12-12-94   |
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